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(19) (CA) **CANADIAN PATENT** (12)

(54) Stable Aminoglycoside/Penicillin Formulations for Injection

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The invention relates to formulations for injection consisting of at least one oil suitable for injection, at least one aminoglycoside and at least one penicillin for administration in human and veterinary medicine, the use of oils suitable for injection for the preparation of stable formulations for injection containing aminoglycosides and penicillins, and the preparation of formulations for injection of this type and novel salts, which are sparingly soluble in water, of aminoglycoside antibiotics.

From the microbiological viewpoint, a product combining penicillins and aminoglycosides would be extremely desirable, since it would then be possible to deal with almost the entire spectrum of Gram-negative and Gram-positive bacteria. Unfortunately, however, at present it is only possible to inject the two active compounds separately at different sites on the body if the intention is to obtain optimal efficacy from the two active compounds. Moreover, the two injection solutions should not be employed together in one syringe before use (recommendations for use given by the manufacturers of aminoglycoside solutions or by I. Carrizosa and D. Kaye, Antimicrobial Agents and Chemotherapy, 13 (3), pages 505-508, (1978)). The reason for this is chemical incompatibility between penicillins and aminoglycosides, as has been described by J. Herderson et al., Amer. J. Hosp. Pharm., 38, 1167 (1981).

Antibiotics of the aminoglycoside series have been used for a long time for controlling bacterial infections in human and veterinary medicine. In diseases of this type, there is a desire, especially in veterinary medicine, for a successful cure to be achieved after only one injection of the active compound. This is quite possible with, for example, penicillins when a

suspension of sparingly soluble penicillin salts is injected into the animals, the active compound in this being only gradually released. This produces an effective level of penicillin in the blood persisting over a prolonged period, and multiple repetition of the injection is unnecessary.

In the case of aminoglycosides which are normally injected in aqueous solution, the biological half-life is relatively short (about 1 hour), so that an injection has to be undertaken several times a day for an infection.

Thus, it would be desirable, and a great relief for the keeper of animals and the veterinarian, if the number of injections during the illness of the animal could be reduced.

Formulations of aminoglycosides for injection which have these properties have not hitherto been known. It is true that, in another connection, drug formulations which release aminoglycosides continuously over a prolonged period have been described. Thus, for example, eye drops which release gentamicin in a delayed manner are protected in U.S.Patents 4,188,373 and 4,115,544. Moreover, plastic or ceramic drug formulations which are implanted in infected bones and which continuously release the aminoglycoside there are known (see, for example DE-OS (German Published Specification 2,815,934, DE-OS (German Published Specification 3,005,350, East German Patent 139,942 or DE-OS (German Published Specification) 2,807,132).

The preparation of sparingly soluble salts of aminoglycosides has already been described too. However, these are likewise only intended for external use and not for formulations for injection. Thus, antibiotic salts which are insoluble in water are claimed in DE-OS (German Published Specification) 2,301,633, according to which the salt is prepared from gentamicin or

polymyxin as the basis and penicillin or cephalosporins as the acids. These salts have the disadvantage that the ratio of aminoglycoside to penicillin derivative is fixed by the molar ratio and it cannot be adjusted to suit the bacterialogically sensible optimum.

Moreover, using an aminoglycoside formulation which releases the active compounds slowly, it would be possible to develop a product combined with β-lactam antibiotics which would be free from the disadvantages of the penicillin/gentamicin salt described above:

The preparation of a product combining aminoglycoside and penicillin derivatives has, in fact, already been disclosed in DE-OS (German Published Specification) 2,756,079, the penicillin being coated with polyvinylpyrrolidone and lecithin. The dried powder is filled into sterile glass bottles and, before use, can be converted into a combination product by adding an aqueous solution of aminoglycoside and shaking. However, the preparation of this product is elaborate and costly and a "ready to use" suspension cannot be prepared thus.

Surprisingly, according to the invention, it is possible for the first time to prepare formulations for injection which contain active compounds from both classes of active compounds and which are chemically stable, so that they can be prepared and employed as a combination product when the active compounds are suspended in an injectable oil in which they do not dissolve.

Accordingly, the invention relates to formulations for injection consisting of at least one oil suitable for injection, at least one aminoglycoside and at least one penicillin for administration in human and veterinary medicine.

Particularly suitable as formulation components from the group of aminoglycosides are gentamicin, sisomicin, etomicin, amikacin, bluensomycin, neomycin, paromomycin, lividomycin, canamycin, dibekacin, nebramy-

cin, ribostamycin, butirosin, kasugamycin, sagamicin, apramycin, verdamicin, xylostasin, destomycin, hygromycin, seldomycin, umtamicin, tobramycin, spectinomycin and fortimicin.

From this group, those which are particularly preferred are, especially, gentamycin, sisomicin, etomicin, amikacin, neomycin, kanamycin, tobramycin and fortimicin.

From the group of penicillins, all biosynthetic or semisynthetic penicillins can be employed, but in particular: benzylpenicillin, phenoxymethylpenicillin, propicillin, phenethicillin, oxacillin, cloxacillin, dicloxacillin, ampicillin, carbenicillin, methicillin, metampicillin, acidocillin, amoxycillin, ticarcillin, ticcercillin, talampicillin, pivampicillin, epicillin, ciclacillin and indamylcarbenicillin.

Likewise ureidopenicillins, such as, for example, mezlocillin, azlocillin and piperacillin.

From this group, those which are particularly preferred are, especially, benzylpenicillin, oxacillin, cloxacillin, dicloxacillin and ampicillin. The substances from the group of aminoglycosides and the penicillins can both be employed in the form of their free acid or base or in the form of their salts. Salts which only dissolve to a slight extent in water and thus bring about a delayed delivery of active compound can also be employed. In the case of penicillins these are, for example, the procaine salts or benzathine salts.

The invention also relates to salts, which are sparingly soluble in water, of aminoglycoside antibiotics and organic carboxylic or sulphonic acids or hemiesters of polybasic inorganic acids with aliphatic alcohols, none of which have antibiotic activity.

Within the meaning of the present invention, the term "sparingly soluble" is to be interpreted as 1 to 1000 mg, preferably 1 to 500, and particularly prefer-

ably 5 to 200 mg of the salt dissolving in 1,000 ml of water at 20°C .

The suitable aminoglycoside antibiotics suitable according to the invention for the salt formation are preferably the following:

Gentamicin, sisomicin, etomicin, amikacin, streptomycin, bluensomycin, neomycin, paromomycin, lividomycin, kanamycin, dibekacin, nebramycin, ribostamycin, butirosin, kasugamycin, sagamicin, apramycin, verdamicin, xylostasin, destomycin, hygromycin, seldomycin, umtamicin, tobramycin, septinomycin and fortimicin.

From this group, those which are particularly preferred are, especially, gentamicin, sisomicin, etomicin, amikacin, streptomycin, neomycin, kanamycin, tobramycin and fortimicin.

Aminoglycosides which are derivatised at their hydroxyl and/or amino groups are also suitable according to the invention. These are, for example, derivatives according to DE-OS (German Published Specification) 2,712,160 (aminoglycosides which have, on at least one N atom, an alkyl or acyl radical having an ether or thioether group), DE-OS (German Published Specification) 2,924,659 (aminoglycosides which have, on at least one N atom, an aminohydroxyalkyl radical), DE-OS (German Published Specification) 2,753,769 (1-N-carbamoyl- and 1-N-alkoxycarbonyl-aminoglycosides), DE-OS (German Published Specification) 2,832,268 (aminoglycosides which have, on at least one N atom, a polyhydroxyalkyl radical), DE-OS (German Published Specification) 2,921,973) (1-N-hydroxyalkylaminoalkyloxycarbonyl-sisomycin), DE-OS (German Published Specification) 2,928,183 (sisomicin which is substituted with secondary alkyl at the 1-N atom), DE-OS (German Published Specification) 3,100,739 (sisomicin substituted by a carbamoyl group at the 5-O atom) and DE-OS (German Published Specification) 3,101,376 (1-hydroxyalkylurethane-sisomicin) and the

pseudodisaccharides according to DE-OS (German Published Specification) 2,730,372.

Suitable as the acid component of the salts according to the invention are all organic carboxylic acids or sulphonic acids and hemiesters of inorganic acids with aliphatic alcohols which do not themselves have antibiotic activity and which form a salt which is sparingly soluble in water with the particular aminoglycoside (derivative). Examples which may be mentioned are as follows:

Embonic acid or pamoic acid (= 4,4'-methylene bis[3-hydroxy-2-naphthalenecarboxylic acid]), 1,5-naphthalenedisulphonate or higher fatty acids, for example dodecanoic acid, tetradecanoic acid, hexadecanoic acid, octadecanoic acid, cerotic acid, oleic acid, elaidic acid, linoleic acid or β-hydroxymyristic acid.

Of these acids, embonic acid and optionally unsaturated fatty acids having 8-25 carbon atoms, in particular 12-18 carbon atoms are preferred. Hemiesters of dibasic or polybasic inorganic or organic acids with aliphatic alcohols, such as monocetyl sulphate or monocetyl malonate or ethyl succinate are also suitable. Hemiesters of long-chain (8-25, preferably 12-18 carbon atoms) alcohols are preferred.

The salts according to the invention are preferably employed in combination with β-lactam antibiotics, it being possible for the latter to be present both in the form of the free acid and in the form of a salt. In this connection, all β-lactam antibiotics which are known per se are suitable according to the invention, for example, penicillins, cephalosporins and oxacephems. The following may be mentioned as examples: ampicillin, propicillin, oxacillin, dicloxacillin, carbenicillin, azidocillin, mezlocillin, azlocillin, penicillin G, procaine-penicillin G, pivampicillin, amoxixillin, flucloxacillin, ticarcillin, carindacilin,

cielacillin, epicillin, cefaloridin, cefalothin, cefazolin, cefamandole, cefoxitin, cefuroxime, cephalexin, cefradine, cefaclor, cefadroxil, thienamycin and cefotaxim.

The sparingly soluble salts of the aminoglycoside antibiotics can be prepared by bringing aqueous solutions of free basic aminoglycosides or their neutral salts with inorganic or organic acids to reaction with aqueous solutions of salts, for example, of higher fatty acids or of embonic acid. As a rule the reaction temperature is in the range between 5° and 95°C, preferably between, 50° and 80°C. The sparingly soluble precipitate which is produced is then filtered off with suction, thoroughly washed with water and dried by customary methods.

Suitable liquid vehicles are oils and lipids which are suitable for injection. Injectable oils or lipids are usually lipids which are liquid at room temperature, for example, groundnut, maize, almond, olive, castor or sesame oil, or fatty acid esters, for example ether oleate or isopropyl myristate, which can be used as solvents for substances to be injected or for the preparation of lipid emulsions to be administered intravenously. They must comply with the regulations relating to "injectables" in the Federal Republic of Germany, that is to say they must be prepared in accordance with the procedures in the pharmacopoeia (in this context, compare also K. Münzel, J. Büchi and O.-E. Schultz, Galenisches Praktikum (Practical Formulation), Wiss. Verlagsges. mbH, Stuttgart (1959) and Arzneibereitung (Drug Formulation), Ferdinand EnkeVerlag, Stuttgart (1969)). According to Swiss Patent Specification 349,750 (dated 4.6.56/15. 12.60; C.1961. 9893), an injectable formulation is prepared, for example, by heating 500 g of olive oil with a mixture of 84 g of glycerol and 5 g of sodium hydroxide at 85°C for 8 hours. The upper phase, which contains monoglycerides and diglycerides, is separated off, washed

and dried. M.M. A. Guerbert (British Patent Specification 181,551 dated 31.8.67, French Patent Specification dated 18.2.64; C. A. 67. No. 120,191 (1967)) recommends, as an injectable lipid base, vegetable oils, their alcoholysis products or halogenated derivatives, in particular combined with polyethylene glycol 400 monopalmitate and a tartaric ester of the monoglycerides of cotton seed oil. The following are also suitable: soya bean oil, miglyol 812®, Viscoleo® and Arlacel A®.

Suitable and particularly preferred are oils or lipids suitable for injection, for example natural triglycerides, such as sesame oil, groundnut oil, castor oil, almond oil, maize germ oil or olive oil, or synthetic triglycerides, such as, for example, a mixture of triglycerides of saturated vegetable fatty acids of medium chain length (C_8-C_{12}), and caprylic/capric acid triglyceride.

Other auxiliaries can be added to the suspension formulation, for example, wetting agents, such as lecithin or polyoxethylene-sorbitan monooleate, thickening agents, such as aluminium monostearate, preservatives, such as phenols, benzyl alcohol or hydroxybenzoic esters.

The proportions of active compounds and auxiliaries used for the preparation of the formulation can vary within the following limits:

The active aminoglycosides can be introduced into the vehicle in a range from 0.5 to 30%, preferably from 1 to 15%, relative to the aminoglycoside base.

The proportion of auxiliaries can vary between 0.05 and 10%, preferably 0.2 to 5%.

The proportion of penicillins in the combined formulation can be between 1 and 40%, preferably 3 to 30%.

The preparation of the suspension ready for injection is carried out under aseptic conditions in a

manner known in pharmacy.

The desired active compounds are precipitated sterile to a specified particle size or the sterile product is ground under aseptic conditions. In this context, the particle size should be between 2 and 60 mcm, but preferably between 5 and 30 mcm.

The ground substance is introduced into the solvent, which has been previously sterilised, and homogenised under aseptic conditions. The homogeneous suspension is filled out under sterile conditions.

The following examples are intended to illustrate, but not restrict, the invention.

The formulation examples detailed below were prepared by the above procedure under a laminar flow hood.

The data relating to the composition are in weight/volume.

Examples

Substances employed	A	B	C	D	E	F	G	H
Etomicin sulphate (≙ 1% base)	1.6 g	1.6 g						
Sodium sulphite	0.2 g							
Water for injection	ad 100 ml							
2% aluminium monostearate gel with sesame oil		ad 100 ml				ad 100 ml		
Etomicin embonate (≙ 1.0 g of base)			3.46 g			3.46 g		
Ethyl oleate			ad 100 ml					
Etomicin hexadecanoate (≙ 1.0 g of base)				4.15 g				
Etomicin dodecanoate (≙ 1.0 g of base)					3.49 g			
Sesame oil				ad 100 ml	ad 100 ml		ad 100 ml	ad 100 ml
Penicillin G Potassium						6.30 g		
Gentamicin embonate (≙ 1.0 g of base)							3.48 g	
Sisomicin pentaembonate (≙ 1.0 g of base)								3.69 g

Example I

a) Composition

Etomicin sulphate, ground and sterile	1.77 g
Penicillin G Potassium, ground	1.55 g (≙ 2.5 mill.U)
Miglyol 812® (= synthetic triglyceride)	ad 100 ml

b) Preparation as described above

c) Stability of the formulation

	Etomicin sulphate determined as base	Penicillin G potassium, Mill.U
Initial content	0.85%	2.36%
Storage at 20°C for 3 months	0.84%	2.44%
Storage at 35°C for 3 months	0.86%	2.37%
Storage at 20°C for 6 months	0.89%	2.37%

Example J

a) Composition

Etomicin sulphate, ground and sterile	1.77 g
Procaine penicillin G, ground and sterile	9.79 g
Aluminium monostearate 2% gel in sesame oil	ad 100 ml

b) Preparation as described above

c) Stability of the formulation

	Etomicin sulphate as base	Procaine penicillin G K
Initial content	0.93%	10.1%
Storage at 20°C for 3 months	0.90%	10.5%
Storage at 35°C for 3 months	0.85%	10.25%
Storage at 20°C for 6 months	1.05%	9.5%

Example K

a) Composition

Sisomicin sulphate	1.77 g
Oxacillin sodium	1.50 g
Tocopherol	0.30 g
Groundnut oil	ad 100 ml

b) Preparation as described above

c) Stability of the formulation

	Sisomicin sulphate calculated as base	Oxacillin sodium
Initial content	1.0%	1.45%
after storage for 1 month in a refrigerator	0.98%	1.42%
at 20°C	1.02%	1.41%
at 30°C	1.07	1.44

Example L

a) Composition

Etomicin sulphate	1.77 g
Ampicillin trihydrate	1.50 g
Lecithin	0.50 g

Ethyl oleate ad 100 ml

b) Preparation as described above

c) Stability of the formulation

	Etomicin sulphate as base	Ampicillin as acid
Initial content	0.97%	1.39%
after storage for 1 month in a refrigerator	0.98%	1.32%
at 20°C	0.99%	1.33%
at 30°C	0.95%	1.22%

Examples of other stable formulations are as follows:

Example M

Etomicin sulphate (corresponding to 3.0 g of base)	5.217 g
Procaine penicillin G	30.000 g
Lecithin	0.1 g
Miglyol 812(R) (synthetic triglyceride)	ad 100 ml

Example N

Gentamicin sulphate (corresponding to 3.0 g of base)	5.115 g
Penicillin G Potassium	30.000 g
Ethyl oleate ad	100 ml

Example O

Gentamicin embonate (corresponds to 2.0 g of base)	7.000 g
Penicillin G potassium	1.550 g

N,N'-dibenzylethylenediamine salt of penicillin G acid	20.000 g
Lecithin	2.000 g
Miglyol 812®	ad 100 ml

Example P

Etomicin embonate (≙ 2.0 g of base)	6.92 g
Etomicin sulphate (≙ 1.0 g of base)	1.60 g
Procaine penicillin G	25.00 g
Lecithin	0.02 g
Caprylic/capric acid triglyceride	ad 100 ml

The levels of the aminoglycoside in the blood using the formulations were determined in the following manner:

The formulations were administered intramuscularly in appropriate doses to beagle dogs. Blood samples were taken at various times after treatment and the serum was taken by centrifugation. The content of active compound in the serum was determined microbiologically using the agar diffusion test (well test). The detecting organism used was the strain Bacillus subtilis ATCC 6633, and the test medium used was DST agar. The content of active compound in the various serum samples were determined on the basis of a standard in buffer. The results (see the Table) show that, after administration of the sparingly soluble salts, therapeutically relevant levels in the blood were achieved over a considerably longer time than with, for example, the corresponding water-soluble sulphates. As a consequence of the marked prolongation of the half-life, these formulations offer crucial advantages for therapy.

Table 1

Levels in dog serum/intramuscular

Formulation examples	Etomicin salt	Dose mg/kg	Half-life (h)	Serum concentration (γ/ml) 1h	8h	12h
B	Sulphate	4	1	9.5	0.2	-
C	Embonate	4	1.8	5	0.7	-
	Sulphate + Embonate	4	2	7.5	0.46	-
E	Dodecanoate	4	2.5	8.8	1.3	0.36
		4	2.3	7.8	0.7	0.1
		1	2	1.4	0.15	-
D	Hexadecanoate	4	3.9	4.4	1.3	0.36
		4	3.9	3.1	0.84	0.45
		1	2.4	2	0.3	-

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A formulation for injection consisting of at least one oil suitable for injection, at least one aminoglycoside and at least one penicillin for administration in human and veterinary medicine.

2. A formulation for injection according to claim 1, which contains 0.5 to 30% by weight of at least one aminoglycoside, 1 to 40% by weight of at least one penicillin and optionally 0.05 to 10% by weight of other formulating auxiliaries.

3. A formulation for injection according to claim 1, wherein the aminoglycoside and the penicillin are present in the form of their bases or salts.

4. A formulation for injection according to claim 1, 2 or 3, wherein the aminoglycoside and the penicillin have particle sizes between 2 and 60 mcm.

5. A formulation for injection according to claim 1, 2 or 3, wherein the aminoglycoside and the penicillin have particle sizes between 5 and 30 mcm.

6. A formulation for injection according to claim 1, 2 or 3 which contains the following pair of active compounds: Etomicin sulphate and Penicillin G Potassium.

7. A formulation for injection according to claim 1, 2 or 3 which contains the following pair of active compounds: Etomicin sulphate and Procaine Penicillin G.

8. A formulation for injection according to claim 1, 2 or 3 which contains the following pair of active compounds: Sisomicin sulphate and Oxacillin sodium.

9. A formulation for injection according to claim 1, 2 or 3 which contains the following pair of active compounds: Etomicin sulphate and Ampicillin trihydrate.

10. A formulation for injection according to claim 1, 2 or 3 which contains the following pair of active compounds: Gentamicin sulphate and Procaine penicillin G.

11. A formulation for injection according to claim 1, 2 or 3 which contains, as the oil, sesame oil, groundnut oil, castor oil, almond oil, maize germ oil, olive oil, a synthetic triglyceride of a saturated C_8-C_{12} vegetable fatty acid or a fatty acid ester.

12. A formulation for injection according to claim 1, 2 or 3 which contains, as formulation auxiliaries, one or more wetting agents, thickening agents or preservatives.

13. A formulation according to claim 1, 2 or 3 which contains 0.5-30% by weight of the salt (calculated as aminoglycoside base) and 1-40% by weight of β-Lactam antibiotic.

14. An ampoule containing a formulation for injection as defined in claim 1, 2 or 3.

15. A process for the preparation of formulations for injection containing an aminoglycosides and a penicillin, wherein the active compounds, separately or together, are precipitated

sterile to a particle size of 2 to 60 mcm or are ground under aseptic conditions and the active compounds thus pretreated are homogeneously suspended in an injectable oil.

16. A process according to claim 15 wherein the active compounds are Etomicin sulphate and Penicillin G Potassium.

17. A process according to claim 15 wherein the active compounds are Etomicin sulphate and Procaine Penicillin G.

18. A process according to claim 15 wherein the active compounds are Sisomicin sulphate and Oxacillin sodium.

19. A process according to claim 15 wherein the active compounds are Etomicin sulphate and Ampicillin trihydrate.

20. A process according to claim 15 wherein the active compounds are Gentamicin sulphate and Procaine penicillin G.

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ABSTRACT OF THE DISCLOSURE

"Stable aminoglycoside/penicillin formulations for injection"

An injectable antibiotic composition comprising an injectable oil, an aminoglycoside and a β-lactam antibiotic. Following injection, the active ingredients remain in the bloodstream for long periods of time.

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